Treatment options and results of adjuvant treatment in nonmuscle-invasive bladder cancer (NMIBC) during the Bacillus Calmette-Guérin shortage

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Abstract: PURPOSE OF REVIEW Given the worldwide shortage of Bacillus Calmette-Guérin (BCG), we review the efficacy of alternative BCG application schedules, doses or strains and intravesical chemotherapy in patients with nonmuscle-invasive bladder cancer (NMIBC). RECENT FINDINGS Modifying BCG schedules by reducing the dose is preferable to reducing the frequency of BCG that increases recurrence rates and should be avoided if possible. Changing the BCG substrain represents a reasonable option, as current evidence does not suggest different oncological outcomes with specific BCG substrains. Mitomycin C (MMC) alone is inferior to BCG with maintenance, but promising results have been demonstrated when used with chemohyperthermia and electromotive drug administration. Several other intravesical chemotherapies including Gemcitabine and Epirubicin should be used when both BCG and MMC are in short supply. SUMMARY In case of BCG shortage, much will depend on the severity and length of the BCG shortage, but our review supports several solutions: First, we recommend contacting the local pharmacist or BCG supplier to consider alternative BCG strains or sterile splitting of BCG doses. In the complete absence of BCG, consideration should be given to MMC with chemohyperthermia or electromotive drug administration where available or other intravesical chemotherapy. High-risk patients should be considered for cystectomy.

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Treatment options and results of adjuvant treatment in Non-Muscle Invasive Bladder Cancer (NMIBC) during the BCG shortage

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ABSTRACT

Purpose of review

Given the worldwide shortage of Bacillus Calmette–Guérin (BCG) we review the efficacy of alternative BCG application schedules, doses or strains and intravesical chemotherapy in patients with non-muscle-invasive bladder cancer (NMIBC).

Recent findings

Modifying BCG schedules by reducing the dose is preferable to reducing the frequency of BCG which increases recurrence rates and should be avoided if possible. Changing the BCG substrain represents a reasonable option as current evidence does not suggest different oncological outcomes with specific BCG substrains. Mitomycin C (MMC) alone is inferior to BCG with maintenance but promising results have been demonstrated when used with chemohyperthermia and electromotive drug administration . Several other intravesical chemotherapies including Gemcitabine and Epirubicin should be used when both BCG and MMC are in short supply.

Summary

In case of BCG shortage much will depend on the severity and length of the BCG shortage but our review supports several solutions: First, we recommend contacting the local pharmacist or BCG supplier to consider alternative BCG strains or sterile splitting of BCG doses. In the complete absence of BCG, consideration should be given to MMC with chemohyperthermia or electromotive drug administration where available or other intravesical chemotherapy. High-risk patients should be considered for cystectomy.

Keywords: bladder cancer, Bacillus Calmette–Guérin, BCG, shortage, gemcitabine, intravesical therapy, mitomycin C

INTRODUCTION

Bladder cancer is the second most common malignancy of the urinary tract and leads to 400'000 new diagnoses and 160,000 deaths per year worldwide with an estimated increase of 40% by 2035 (1). Around 75% of patients with bladder cancer have non-muscle-invasive bladder cancer (NMIBC) for which the cornerstone of management currently is transurethral resection of the bladder (TURB) (2). Current guidelines recommend the use of intravesical Bacillus Calmette– Guérin (BCG) in patients with intermediate to high-risk NMIBC to reduce the risk of recurrence and progression (2, 3). It has been estimated that the global demand for BCG is up to 2 million doses per year but Merck (Kenilworth, NJ, USA) the current global market leader can only produce 700,000 doses globally. Closures of BCG plants in 2012 and 2014, reduction of production in 2015 and the withdrawal of a large BCG manufacturer in 2017 has led to sustained worldwide shortages of BCG. Given the methodological complexity and high demands of BCG production future shortages are to be expected (4). In this report, we briefly review alternative BCG application schedules, doses, strains and intravesical therapies and provide recommendations for periods of BCG shortage.

METHODS

We conducted a literature search on using the Medline database. For our literature research, we used combinations, synonyms and related search terms to "bladder" and "cancer" and "nutrition" or "lifestyle" and selected the time period between 1st of November 2017 until November 18th 2019. The following search terms were used: (((((("2017/11/01"[Date - Publication] : "3000"[Date - Publication])) AND ((((bladder[Title/Abstract] OR urothel*[Title/Abstract]) AND (cancer*[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR neoplasm*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract])) AND Bcg[Title/Abstract])))))). Non-English literature, animal studies, case reports and correspondence/letters were excluded.

CHANGE OF BCG SCHEDULE

During a period of BCG shortage the standard BCG schedule of full dose induction followed by up to 3 years of maintenance BCG can be adapted. Broadly there are three options 1) Reduce the dose of each instillation 2) Shorten the length of the BCG course 3) Reduce the number of instillations per maintenance cycle.

1) Reducing the dose of each instillation

Based on the results of an EORTC-GU group trial patients could be treated with a one third dose of BCG for induction and maintenance. This was not inferior to full dose BCG for progression or overall survival although it was associated with a higher recurrence rate (5). This approach does have logistical challenges: unlike a standard vial of full dose BCG it is not possible to prepare one third dose BCG using a closed system and preparation of the BCG will most likely need to be carried out under aseptic conditions in pharmacy. Concerns have been raised about suboptimal dosing in patients but it should be pointed out that as an example, each vial of TICE BCG (Merck, Kenilworth NJ, USA) contains between 1-8x10^8 CFU, an eightfold difference. Given this wide variation in CFUs that already exists in a single vial, splitting this into a third will not necessarily result in suboptimal dosing. However one third dose seems to be the minimum dose for clinical effectiveness as it has been shown that one sixth dose BCG was inferior to one third dose BCG (6). Furthermore, the split dose BCG cannot be stored overnight and should ideally be used within 2 hours so 3 patients will need to be treated at the same time which is logistically difficult although up to 8 hours is feasible to "share" the same vial and stagger treatment timings (personal communication, A.Kamat, Houston, USA).

2.) Shorten the length of the BCG course

Although a maintenance course of BCG is the current standard of care, an induction course of BCG alone may be considered if dose splitting is impossible and intravesical chemotherapy is not available. Herr et al. have shown that when an induction course of 6 BCG instillations is

given alone, only one third of patients required a further course of BCG. However an 11% 5 year progression rate was seen which is higher than when maintenance BCG is used (7). Therefore if BCG supplies allow it maintenance BCG should always be given and it is probably better for a patient to receive one third dose BCG induction and 12 maintenance instillations over 18 months, which requires a total equivalent of 6 vials, than the same number of vials as full dose BCG induction only.

The EORTC-GU group have shown that reducing the length of maintenance from 3 years to 1 year has no effect on progression or death but is associated with an increased recurrence rate (5). However patients with CIS should still be offered 3 years of maintenance (at a reduced dose of one third if necessary) (8).

3.) Reducing the number of instillations per maintenance cycle

Although this may appear to be an attractive option when compared to the difficulties associated with preparing a reduced dose, it has been shown that a single instillation per maintenance cycle for 3 years is no better than an induction course alone (6). Furthermore the EAU Research Foundation recently halted the NIMBUS trial, a randomized trial studying the effects a reduced number of instillations following a safety analysis by the independent data monitoring committee showing that a reduced instillation schedule was inferior to a standard instillation schedule (9)

CHANGE OF BCG STRAIN

Given the genetic difference between BCG substrains several clinical trials and meta-analyses have studied whether substrains differ regarding oncological outcomes. However, only a limited number of sufficiently powered trials with head-to-head comparisons have been published (10). The current literature has been summarized by several meta-analyses with diverging results. A network meta-analysis which aimed to simulate direct comparisons between substrains suggested that BCG is superior compared to intravesical chemotherapy only but no single substrain was superior compared to the others BCG substrains (11). In

contrast, a meta-analysis without network comparisons suggested that patients treated with TICE had a higher risk of recurrence compared to Connaught or RIVM (12). This currently limited evidence will be improved by two interesting trials. The first ongoing trial was started because TICE BCG became the predominant strain in the USA. As a consequence, the Southwest Oncology Group has launched the S1602 trial comparing TICE BCG to the Tokyo substrain, and tests whether subcutaneous inoculation of BCG will improve oncologic responses(13). The second ongoing trial is a phase I/II trial which will assess the safety and efficacy of recombinant BCG VPM1002BC (NCT02371447). In absence of clear evidence regarding superior efficacy of one specific substrain, we recommend that during BCG shortage Urologists should discuss with their BCG provider or pharmacist whether alternative BCG substrains can be provided.

INTRAVESICAL CHEMOTHERAPY

In view of the interruptions to BCG supplies over the past years, several intravesical chemotherapies have been studied.

Mitomycin C

Intravesical mitomycin C (MMC) is the most extensively investigated chemotherapy agent in patients with NMIBC. An individual patient data meta-analysis of nine randomized controlled trials suggested a 32% higher risk of recurrence following MMC when compared to BCG maintenance but conversely a 28% reduction in risk of recurrence when compared to BCG induction alone. It is perhaps worth emphasizing that there were no significant differences in disease progression, cancer-specific survival and overall survival (14). Another advantage of MMC compared to BCG is that is has fewer side effects (15).

Chemohyperthermia with Mitomycin C

A randomized study comparing radiofrequency-induced chemohyperthermia using MMC with BCG showed promising 24-month recurrence-free survival rates of 78% and 65% respectively (p=0.08) (16). Another randomized study compared between radiofrequency-

induced chemohyperthermia using MMC (6-weekly induction instillations, followed by maintenance instillations at 6-week intervals for the first year and at 8-week intervals for the second year) and BCG (induction and maintenance for one year) in patients with recurrent intermediate- and high-risk NMIBC following induction and/or maintenance BCG (17). Overall, there were no differences in complete response at 3 months and disease-free survival between the two groups. However, subgroup analyses showed that patients with CIS had a lower disease-free survival with chemohyperthermia. The HIVEC 1&2 trials investigating the use of conductive chemohyperthermia are currently under way (18).

Electromotive MMC and sequential BCG

One randomized study investigated the use of electromotive MMC and sequential BCG induction and maintenance in patients with T1 bladder cancer (19). Patients in the sequential treatment group showed significantly lower recurrence (42% vs 58%), progression (9% vs 22%, disease-specific (6% vs 16%) and overall mortality (22% vs 32%) rates than the BCG-alone group. The sequential use of electromotive MMC and BCG can also reduce the total amount of BCG being used (9 doses vs 16 doses per patient), however, it is challenging due to logistical reasons and a relatively complicated treatment schedule.

Gemcitabine

There were two randomized trials comparing between intravesical gemcitabine and BCG in BCG-naïve NMIBC. In the first study by Bendary *et al.* (20), patients with primary Ta or T1 disease without CIS were randomized to receive six weekly intravesical instillations of either gemcitabine or BCG. There were no significant differences in the recurrence and progression rates between the two groups. In the second study by Porena *et al.* (21), patients with high-risk NMIBC were randomized to receive three years of either gemcitabine or BCG. Patients in the gemcitabine group had a higher recurrence rate than the BCG group (53% vs 28%). None of the patients developed disease progression.

Epirubicin

Two randomized trials compared epirubicin with BCG showed inferior oncological outcomes with epirubicin. The first trial including intermediate- and high-risk NMIBC patients who received up to three years of BCG had lower risks of recurrence, distant metastasis, bladder cancer-specific mortality and overall mortality than those who received up to three years of intravesical epirubicin (22). In a second trial comparing BCG with the combination of epirubicin and interferon-α2b, a better disease-free survival was observed in the BCG group (23).

Other chemotherapy agents

The use of other chemotherapy agents including doxorubicin (24), valrubicin (25), pirarubicin (26) and docetaxel (27) has been proposed in the literature. However, data regarding their efficacies and how they compare with BCG therapy are very limited. Further high-quality studies will be needed before these agents can be recommended.

CYSTECTOMY

High-risk NMIBC is a difficult disease to manage, and the progression rate can be up to 17% at one-year and 45% at 5 years (28). Moreover, in patients with T1G3 disease, the pathology is upstaged to muscle-invasive disease in over 50% (29, 30). In a retrospective cohort study, patients with T1G3 disease receiving early cystectomy had a better 10-year cancer-specific survival of 78% compared to 51% in those receiving deferred cystectomy (30). The BRAVO prospective randomized trial comparing radical cystectomy and BCG therapy in high-risk NMIBC was closed due to poor accrual (31, 32). In case of BCG shortage, upfront cystectomy should be discussed in case of high-risk NMIBC.

CONCLUSION

In conclusion, the severity and length of BCG shortages and the availability of alternative options will influence the choice of therapy in each country and hospital. Based on our review we recommend early liaison with the local pharmacist and BCG supplier to consider alternative BCG strains or sterile splitting of BCG doses. In the complete absence of BCG, consideration should be given, where available, to MMC or alternative intravesical chemotherapies. Last but not least, upfront cystectomy should be discussed with high-risk NMIBC patients.

KEY POINTS

- During times of BCG shortage, reducing the dose of BCG to one third can allow a maintenance BCG schedule to be given but will have logistical implications.
- Dose reduction is preferable to an induction course of full dose BCG alone or reducing the number of instillations which should be avoided.
- MMC is inferior to BCG maintenance in terms of recurrence rate, but better than BCG induction alone.
- Intravesical chemotherapies such as Gemcitabine and Epirubicin should be used when both BCG and MMC are in short supply.
- Upfront cystectomy should be discussed with high-risk NMIBC patients in severe BCG shortage

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Conflicts of interest

There are no conflicts of interests.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the period of review, have been highlighted as:

Of outstanding interest:

•• *Tan WS, Panchal A, Buckley L, Devall AJ, Loubiere LS, Pope AM, et al. Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. Eur Urol. 2019;75(1):63-71.*

Comment: This randomised trial in a population of patients with BCG failure demonstatrated that randomisation was feasable and indeed probably essential in this setting.

Of special interest:

• *D'Andrea D, Gontero P, Shariat SF, Soria F. Intravesical bacillus Calmette-Guerin for bladder cancer: are all the strains equal? Translational andrology and urology. 2019;8(1):85-93.*

Comment: This review article summarizes all available literature about the efficacy of BCG substrains.

• *Tan WS, Kelly JD. Intravesical device-assisted therapies for non-muscle-invasive bladder cancer. Nature reviews Urology. 2018;15(11):667-85.*

Comment: This review article summarizes the available literature about intravesical device-assisted therapies in NMIBC.

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